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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,838	FIKSTAD ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,42-52,54-61 and 65-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,42-52,54-61,65-82* is/are rejected.

7)☒ Claim(s) *35 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *25 September 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 35, 42-52, 54-61 and 65-82 are presented for examination.

Applicant's Amendment filed October 10, 2006 has been received and entered into the present application. Accordingly, the specification at page 1, following the title, has been amended.

Claims 35, 42-52, 54-61 and 65-82 are pending and under examination. Claims 36-41, 53 and 62-64 are cancelled, claims 65-82 are newly added and claims 35, 42, 48-51 and 59-60 are amended.

Applicant's Information Disclosure Statement (IDS) filed September 25, 2006 has been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08A (one page total), the Examiner has considered the cited references.

Applicant's arguments, filed October 10, 2006, and amendments to the claims have been fully considered. Applicant's statement that the instant application and the '192 patent were subject to common ownership at the time of the invention has been noted. Accordingly, the rejection set forth under 35 U.S.C. 103(a) is properly withdrawn since the '192 patent is no longer available as prior art under the provisions of 35 U.S.C. 103(c). Rejections and objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and objections are either reiterated or newly applied. They constitute the complete set of rejections and objections presently being applied to the instant application.

Objection to the Claims (New Grounds of Objection)

Claim 35 is objected to because a duplicate semi-colon appears at line 12 of the claim in the limitation "...succinate; ; and a release modulator...".

Claim 60 is objected to for concluding with two periods.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

(New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 47-52, 59 and 72-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Present claim 35, and the claims dependent therefrom, read upon a pharmaceutical composition comprising a therapeutically effective amount of cilostazol; a solubilizer selected from the group consisting of polyoxyl 40 castor oil, polyoxyl 35 castor oil, etc. (claim 35, lines 3-11); and a release modulator which synchronizes the release of the drug and the solubilizer.

In particular, the specification as originally filed fails to provide adequate written description for the claim limitation directed to "a release modulator which synchronizes the release of the drug and the solubilizer" (claim 25).

Applicant has amended the claim from "a release modulator" to now read upon the use of "a release modulator which synchronizes the release of the drug and the solubilizer". Such an amendment now limits the genus of "release modulators" only to those that are capable of performing the function of synchronizing the release of the drug and the solubilizer. In other words, Applicant's claims are now directed to a genus described in terms of a required function (i.e., release synchronization of drug and solubilizer).

MPEP §2163 recites, "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice,

reduction to drawings, or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus." Please reference *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regarding the limitation of "a release modulator which synchronizes the release of the drug and the solubilizer" (claim 25), the broad genus of "release modulators" capable of performing this function of synchronizing the release of both the drug and the solubilizer embraces widely variant species, including but not limited to, devices (e.g., osmotic pumps), slowly dissolving salts or complexes, hydrolysable esters, erodible matrices (e.g., polyamides), polyesters, ion exchange resins, waxes (e.g., yellow wax, white wax, carnauba wax, cetyl ester wax), fatty acids or fatty alcohols (e.g., hydrogenated vegetable oils, lauroyl macrogol-32 glycerides), tocol derivatives (e.g., mono-, di- or tri-methyl tocols, PEG-ylated tocols) or polymeric materials (e.g., cellulosics, vinyl polymers, acrylic polymers, methacrylate polymers, polyvinylpyrrolidone copolymers, polysaccharide gums, glycuronan polymers, etc.). Please see the specification at page 14, line 17-page 16, line 6. It has been held that when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The instant specification provides a non-limiting definition and description of a variety of release modulators that Applicant states are known to those of ordinary skill in the art and are encompassed by the present claims. However, the specification does not provide disclosure of relevant identifying characteristics, such as a structure or other physical or chemical properties, or functional characteristics beyond the generic disclosure of synchronizing release of the drug and the solubilizer that is sufficient to demonstrate that Applicant was in possession of the entire genus of release modulators capable of synchronizing the release of both the drug and the solubilizer. Please see *Eli Lilly*, 119 F.3d at 1568, 43

USPQ2d at 1406 and MPEP §2163.

While it is duly noted that the genus of "release modulators" is limited to those 'release modulators' capable of synchronizing the release of the drug and the solubilizer, it remains that Applicant has not appropriately defined the metes and bounds of the genus, even when limited by function (step-plus-function form). MPEP §2163 teaches that step-plus-function claims are adequately described if "the written description adequately links or associates adequately described particular structure, material, or acts to the function recited in a step-plus-function claim limitation," or if "it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a step-plus-function limitation." The instant application does not meet either of these criteria. The present specification provides no disclosure beyond the exemplary release modulators, of which only a few species of each type are disclosed, that would provide a means for identifying materials, other than those specifically disclosed by Applicant, that would have been amenable for use in the present invention, nor does it teach the specific structure, physical properties or a method of identification of such compounds that perform the function recited in the claim. Furthermore, it has been held that a wish or plan for obtaining the chemical invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

While it is recognized that adequate written description of a limitation is not required to be stated *in haec verba* in the specification or claims as originally filed, adequate written support for claim limitations must arise from either an explicit or implicit suggestion by the disclosure to show that such a concept as claimed was actually in possession of Applicant at the time of the invention. For the reasons provided *supra*, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means that fully set forth the claimed invention,

in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the entire genus of release modulators capable of synchronizing the release of the drug and the solubilizer.

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Claims 42-44, 46, 66-68 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Present claim 42 is directed to a variety of release modulators to be incorporated into the pharmaceutical composition comprising cilostazol in a therapeutically effective amount in combination with a solubilizer, of which is a "tocol derivative" is a specifically claimed release modulator (claim 42, line 4).

In particular, the specification as originally filed fails to provide adequate written support for the claim limitation directed to "a tocol derivative".

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications* under the 35 U.S.C. 112.1 "Written Description" Requirement ("*Guidelines*"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of

sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant discloses at the paragraph bridging pages 15-16 of the instant specification, "Specific examples of tocol derivatives useful as release modulators include, but are not limited to, the mono-, di-, trimethyl- tocols, commonly known as tocopherols, and the organic acid esters thereof (*e.g.*, acetate, nicitanoate, succinate, polyethylene glycol succinate esters, *etc.*). For example, alpha-tocopherol, alpha-tocopherol acetate, alpha-tocopherol nicotinate, alpha-tocopherol succinate, alpha-tocopherol polyethyleneglycol (200-8000 MW) succinate, alpha-tocopherol polyethyleneglycol 400 succinate are specific compounds useful as release modulators. The mixed racemic forms (*e.g.* all racemic or dl-), and the pure enantiomers (*e.g.* d-, l- or RRR-) of tocol derivatives are all useful in practicing the current invention."

Applicant has failed to provide sufficient written description to support the use of "a tocol derivative". In fact, the present disclosure fails to recite any structural characteristics, chemical formula, name(s) or physical characteristics such that one of ordinary skill in the art would have been able to readily identify the scope of those compounds encompassed by the term "a tocol derivative." Though the disclosure provided above has been noted, such teachings provide only an exemplary and non-limiting teaching of what tocol derivative compounds would be considered within the scope of the term "a tocol derivative".

While it may be construed that the fact that the compound is based upon the parent tocol compound structure implies some sort of chemical or structural characteristics sufficient to fulfill the

written description requirement of 35 U.S.C. 112, first paragraph, it is herein noted that Applicant has failed to describe in any certain terms the degree of derivation or similarity that a compound may have from tocol and still be considered a derivative for use as a release modulator of the claimed composition. The mere fact that the only chemical or structural characteristic of the compound is that it is a derivative of tocol, wherein the degree of similarity or derivation from tocol is herein undefined in the accompanying specification, is not sufficient to provide an adequate description of the genus of compounds intended by Applicant for use in the present invention. In the absence of such description, Applicant's limitation to "a tocol derivative" is not sufficiently supported by the present disclosure in such a way as to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

Considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set forth the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the genus of derivative forms of tocol.

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35, 42-52, 59-61, 65-76 and 82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claims 35, 59 and 60 (and the claims dependent therefrom) are directed to a pharmaceutical composition comprising a therapeutically effective amount of a drug, a solubilizer selected from the group consisting of polyoxyl 40 castor oil...caprylic acid mono/diglycerides, and mono- and diacetylated monoglycerides, linoleoyl monoglycerides...alpha-tocopherol polyethyleneglycol (200-8000 MW) succinate...and d-alpha-tocopherol polyethyleneglycol 1000 succinate; and a release modulator which synchronizes the release of the drug and the solubilizer.

In particular, it is noted that the limitation "caprylic acid mono/diglycerides, and mono- and diacetylated monoglycerides" renders the scope of the claim indefinite because it is unclear whether the claim intends to encompass the use of caprylic acid monoglycerides, caprylic acid diglycerides, caprylic acid monoacetylated monoglycerides or caprylic acid diacetylated monoglycerides ***or*** whether the claim intends to encompass the use of caprylic acid monoglycerides, caprylic acid diglycerides, monoacetylated monoglycerides or diacetylated monoglycerides. In other words, the manner in which the claim is written does not clearly set forth whether the limitation "mono- and diacetylated monoglycerides" is intended to modify the preceding limitation of "caprylic acid mono/diglycerides" or whether it is intended to stand alone as a separate and distinct type of solubilizer. For these reasons, one of ordinary skill in the art would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is seeking protection.

Further, it is noted that present claim 35 recites the use of the solubilizer "alpha-tocopherol polyethyleneglycol (200-8000 MW) succinate". The recitation of the parenthetical limitation "(200-8000 MW)" renders the scope of the claims indefinite because Applicant has failed to delineate how this limitation is intended to limit the claim. For example, it is not clear whether this limitation is meant to restrict the alpha-tocopherol polyethyleneglycol succinate compound only to those that are of molecular weights 200-8000 or whether such molecular weights are intended to be exemplary of the types that may be employed within the presently claimed pharmaceutical composition. For these reasons, one of

ordinary skill in the art would not have been reasonably apprised of the scope of alpha-tocopherol polyethyleneglycol succinate compounds that Applicant intends to presently claim.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 42-43, 45, 66-67 and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claims 42-43, 45, 66-67 and 69 each recite the limitation "racemers, enantiomers, or mixtures thereof".

In particular, it is noted that it is not clear to what the limitation "racemers, enantiomers, or mixtures thereof" refers. Specifically, the limitation directed to, for example, "a tocol derivative" in present claim 42 is separated from the limitation "racemers, enantiomers, or mixtures thereof" and, thus, does not clearly delineate on the record whether the racemers, enantiomers or mixtures thereof are intended only to apply to, for example, the tocol compounds or whether the racemers, enantiomers or mixtures thereof applies to any one or more of those release modulators that are named in the claim. Furthermore, if one of ordinary skill in the art at the time of the invention were to understand the phrase "racemers, enantiomers, or mixtures thereof" to apply to any one or more members of the claimed list of agents, then what kind of compounds would be encompassed by a racemic wax, for example, or an enantiomeric erodible matrix?

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 72-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 72 is directed to the dosage form of claim 47, "wherein the period of time is more than 1 hour." Present claim 73 is dependent upon claim 72 and further limits the period of time to more than 2 hours. Present claim 74 is dependent upon claim 73 and further limits the period of time to 2-24 hours.

In particular, present claim 72 is dependent upon claim 47, which is directed to a pharmaceutical composition, not a dosage form. Accordingly, the scope of the claim is indefinite because the claim does not clearly set forth the subject matter that it is intended to further limit. It is unclear whether present claims 72-74 are intended to limit the dosage form as defined by present claim 60 or they are intended to further limit the pharmaceutical composition as defined by, e.g., present claim 35. Accordingly, the metes and bounds of the subject matter for which Applicant is presently seeking protection is not clearly and precisely set forth.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

For the purposes of examination, present claim 72 will be interpreted as being dependent upon claim 60.

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35, 42-45, 51-52, 54-56, 59-61, 65-69, 75-79 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amselem et al. (U.S. Patent No. 5,891,469; 1999) in view of The Merck Index (Eleventh Edition, Monograph 2277, 1989; Pages 353-354).

Amselem teaches pharmaceutical compositions capable of increasing the oral bioavailability of a lipophilic substance (col.5, lines 49-5), comprising: (1) a lipophilic substance that possesses low water solubility and poor oral bioavailability (col.1, lines 21-22), such as a steroid or coenzyme Q10 (i.e., a benzoquinone), (2) the surfactant alpha-tocopherol polyethylene glycol succinate (also meets Applicant's limitation directed to "tocopherol succinate", see, e.g., present claim 54), usually with a mean molecular weight of 1000 (col.5, lines 49-66), and further (3) at least one dispersion adjuvant, such as tocopherol acetate, polyvinylpyrrolidone, a medium or long chain triglyceride and/or polyethylene glycol (col.6, lines 23-26 and col.6, lines 58-66). Amselem also teaches that the disclosed composition may be administered in a therapeutically effective amount to a mammal in need of such a substance (see claim 19; col.14), wherein the substance may be in a gelatin capsule or tablet unit dosage form (see claims 9-10; col.14) and may also further comprise any suitable nontoxic carrier or diluent powder or additive (col.7, l.4-15). Amselem further teaches that the lipophilic substance is present from 0.01-50% of the total solid weight of the composition, the surfactant TPGS is present from 5-65% of the total solid weight of the

composition and the dispersion adjuvant is present from 5-75% of the total solid weight of the composition (col.6, lines 37-57).

The teaching of tocopherol polyethyleneglycol (PEG) succinate, especially tocopherol polyethyleneglycol 1000 succinate, as the surfactant component of the disclosed pharmaceutical composition places the use of either the racemic or either enantiomeric form (d- or l-) of tocopherol PEG succinate clearly within the possession of the public. Furthermore, though Amselem et al. does not expressly recognize the "release modulating" properties of the, e.g., tocopherol PEG succinate, tocopherol acetate, polyvinylpyrrolidone, or medium or long chain triglyceride, the very teaching of the identical chemical entity in overlapping amounts clearly indicates that whatever release modulating properties that Applicant has attributed to either of these compounds are necessarily present, absent factual evidence to the contrary, since chemical compounds cannot have mutually exclusive properties. Please reference MPEP §2112.01.

Amselem et al. broadly teaches the use of the disclosed formulation for solubilizing a lipophilic, i.e., low water solubility and poor oral bioavailability, drug, but fails to disclose cilostazol as the active pharmaceutical agent of the disclosed formulation. However, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ cilostazol in the formulation of Amselem et al. because, as The Merck Index teaches, this antithrombotic agent was well known in the art to be practically insoluble in water (see Monograph 2277) and, therefore, the inclusion of such a compound in the formulation of Amselem et al. would have raised the reasonable expectation of success that such a compound could be effectively solubilized in the disclosed manner for the formulation of an efficacious dosage form. Such a person would have been motivated to use cilostazol in the composition of Amselem et al. because the skilled artisan would have sought ways to enhance the therapeutic effect, and, thus, therapeutic benefit, and bioabsorption of the poorly solubilized and poorly absorbed compound

cilostazol in order to administer a therapeutically effective dosage amount in fewer doses and with less frequency while at least maintaining a similar, if not enhanced, efficacy in the patient being treated.

With regard to present claims 51 and 75, which are directed to the synchronized release of cilostazol and solubilizer with a correlation coefficient of greater than 0.80, such correlation values are, absent factual evidence to the contrary, present in the reference because Amselem et al. teaches the formulation of the lipophilic drug with the surfactant and dispersion adjuvant compounds in clearly overlapping amounts and, thus, in the same ratios as presently claimed to produce a composition that is substantially the same as that presently claimed. In other words, the fact that Amselem et al. teaches identical components in identical, or at the very least, overlapping, amounts is clearly indicative of the fact that any release characteristics attributed to such a composition would be necessarily present in the prior art of Amselem et al., absent factual evidence to the contrary. Please see MPEP §2112.01[R-3] ("Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)).

Claims 35, 42-52, 57, 59-61, 66-76, 80 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. (U.S. Patent No. 5,342,625; 1994) in view of The Merck Index (Eleventh Edition, Monograph 2277, 1989; Pages 353-354), Myers (U.S. Patent No. 5,891,845; 1999) and Lambert et al. (U.S. Patent No. 6,458,373; Issued 2002, Filed 1998).

Hauer et al. teaches pharmaceutical compositions of cyclosporine (a highly hydrophobic drug; col.3, l.22-39) that demonstrate an enhancement of resorption/bioavailability levels, as well as reduced

variability in resorption/bioavailability levels in patients receiving cyclosporine therapy (col.5, l.14-31), which contain a microemulsion preconcentrate of cyclosporine, comprised of (1) a hydrophilic phase, (2) a lipophilic phase (that contains the cyclosporine) and (3) a surfactant phase, wherein the surfactant phase may contain either a single surfactant or mixture of surfactants (col.12, l.16-22), e.g., polyoxyethylene glycolated natural or hydrogenated vegetable oils (i.e., CREMOPHOR RH 40 or CREMOPHOR EL, etc.; col.9, l.48-col.10, l.13); polyoxyethylene(20) sorbitan monopalmitate, polyoxyethylene(20) sorbitan monostearate, polyoxyethylene(20) sorbitan monooleate (col.10, l.14-30); mono-, di- and mono/diglycerides (i.e., caprylic/capric acid mono- and di-glycerides; col.11, l.36-52); sorbitan monolauryl or sorbitan monooleyl (col.11, l.53-58); glyceryl monooleate, glycerol monopalmitate, or glycerol monostearate (col.11, l.64-col.12, l.4), etc. Hauer et al. further teaches the additional inclusion of thickening agents into the composition, such as, e.g., polyacrylate and polyacrylate co-polymer resins (i.e., polyacrylic acid and polyacrylic acid/methacrylic acid resins, etc.; col.12, l.56-64); celluloses and cellulose derivatives (i.e., methyl-, ethyl-, and propyl-celluloses, hydroxypropylcellulose, etc.; col.12, l.65-col.13, l.12); polyvinylpyrrolidone copolymers (col.13, l.13-21); polyvinyl resins (i.e., gum traganth, gum arabicum, etc.; col.13, l.22-25), etc. Hauer et al. discloses the inclusion of one or more additional ingredients, including tocopherols, e.g., alpha-tocopherol (vitamin E), and teaches that the use of an anti-oxidant, in particular a tocopherol, is particularly advantageous (col.13, l.44-50). Hauer et al. teaches the following amounts of the active components for oral dosage forms (col.17, l.26-28): the cyclosporine component in an amount of 1 (or 2) to about 30% of the total weight of the composition (col.17, l.29-31), surfactant components in an amount of from about 20-90% of the total weight of the composition (col.18, l.3-12) and the thickening agents, when present, in an amount of 0.5 (or 5) up to 15 (or 20)% by weight of the total composition (col.20, l.7-13). Production of the disclosed pharmaceutical compositions may be made for filling said composition into gelatin (e.g, soft or hard) capsules (col.24, l.22-30).

Though Hauer et al. teaches the disclosed pharmaceutical compositions for formulating the highly hydrophobic drug cyclosporine, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use such a delivery preparation for the formulation of other highly hydrophobic drugs (i.e., those with low water solubility and, thus, poor bioavailability), such as cilostazol, because, as The Merck Index teaches, this antithrombotic agent was well known in the art to be practically insoluble in water (see Monograph 2277). Accordingly, in view of the extensive hydrophibicity of both cyclosporine and cilostazol, the skilled artisan would have had a reasonable expectation of success in effectively solubilizing cilostazol in the delivery vehicle disclosed by Hauer et al. because of the demonstrated success in effectively solubilizing the hydrophobic agent cyclosporine in such a formulation. Further, such a person would have been motivated to do so in order to enable effective dosing of cilostazol with concomitant enhancement of resorption and bioavailability levels, reduced variability in resorption and bioavailability levels and also a concomitant reduction in the amount required to achieve effective dosing.

With regard to present claims 51 and 75, which are directed to the synchronized release of cilostazol and solubilizer with a correlation coefficient of greater than 0.80, such correlation values are, absent factual evidence to the contrary, present in the reference because Hauer et al. teaches the formulation of the active agents in clearly overlapping amounts and, thus, in the same ratios as presently claimed to produce a composition that is substantially the same as that presently claimed. In other words, the fact that Hauer et al. teaches identical components in identical, or at the very least, overlapping, amounts is clearly indicative of the fact that any release characteristics attributed to such a composition would be necessarily present in the prior art of Hauer et al., absent factual evidence to the contrary. Please see MPEP §2112.01[R-3] ("Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252,

1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)).

Though Hauer et al. does not explicitly teach the release of the active agent over an extended period of time [i.e., more than 1 hour (claims 48 or 72), more than 2 hours (claims 49 or 73), or from 2-24 hours (claims 50 or 74)], Myers (U.S. Patent No. 5,891,845; 1999) teaches the advantages of controlled release formulations to improve the therapeutic value of the active drug component by reducing the ratio of the maximum and minimum plasma levels (Cmax/Cmin) while maintaining such levels within the therapeutic window so as to sustain drug levels as constant effective concentrations (col.5, l.46-61) and further teaches commonly used controlled release systems, such as, e.g., dissolution and diffusion control, ion-exchange resins, osmotic devices, slow dissolving salts or complexes, or pH independent formulations (i.e., those impregnated with water insoluble waxes, such as fatty acids, carnuba wax, beeswax, or polymers, etc.; col.5, l.62-col.6, 15). In view of such teachings, one of ordinary skill in the art would have found it *prima facie* obvious to use any one or more of these well known controlled release systems in order to effect a controlled release profile of the disclosed pharmaceutical composition. Such a person would have been motivated to do in order to sustain therapeutically efficacious levels of the active agent with a concomitant reduction in the amount and frequency of dosing. The determination of the optimal range of time over which the active agent is released would have varied significantly depending on the amount to be administered, the severity of disease, the intensity of the therapeutic effect desired, toxicological and metabolic considerations, and patient compliance with a prescribed regimen. Accordingly, such a determination would have been well within the purview of, and *prima facie* obvious to, the skilled artisan and the presently claimed time ranges are not seen to be inconsistent with those that would have been determined by one of ordinary skill in the art, absent factual evidence to the contrary.

Further, in view of the fact that Hauer et al. broadly teaches the advantage of including a tocopherol as an antioxidant of the disclosed formulation (col.13, l.44-50), one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to include various tocopherol compounds into the disclosed formulations, such as those disclosed by Lambert et al. (U.S. Patent No. 6,458,373; Issued 2002, Filed 1998), e.g., alpha-tocopherol acetate, alpha-tocopherol succinate, alpha-tocopherol nicotinate, tocopherol polyethylene glycol succinate (col.5, l.10-14, col.22, l.54-57), with the reasonable expectation of success that each of these tocopherol compounds would have retained the same or substantially similar antioxidative activity to that of alpha-tocopherol itself. Additionally, the fact that Lambert et al. teaches such alpha-tocopherol compounds as biocompatible surfactants used for the solubilization of poorly water-soluble (i.e., hydrophobic) drugs would also have motivated one of skill in the art to include any one or more of such tocopherol compounds into the formulation because such a person would have expected that the presence of such compounds would have enhanced the solubilization of the active agent, thus, resulting in a more uniform and bioavailable final product.

Claims 35, 42-52, 57-61, 66-76 and 80-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hauer et al. (U.S. Patent No. 5,342,625; 1994) in view of The Merck Index (Eleventh Edition, Monograph 2277, 1989; Pages 353-354), Myers (U.S. Patent No. 5,891,845; 1999), Lambert et al. (U.S. Patent No. 6,458,373; Issued 2002, Filed 1998) and Royce (U.S. Patent No. 5,403,593; 1995).

Hauer et al., The Merck Index, Myers and Lambert et al. as applied above.

Royce teaches the use of the lipid-based glycerol ester surfactants, including, e.g., glycerol palmitostearate, glycerol distearate, etc. (col.4, l.32-50), and waxes, including, e.g., microcrystalline wax (col.4, l.67-col.5, l.2) in the formulation of therapeutically-active sustained-release type pharmaceutical preparations (abstract).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ any one or more of the glycerol ester type surfactants or wax components taught by Royce for use in preparing pharmaceutical preparations with a sustained, or controlled, release profile with the reasonable expectation that the use of such compound(s) would further enhance the solubilization of the hydrophobic agent. Such a person would have been clearly motivated to do so because of the desire to enhance the bioavailability and bioabsorption of the hydrophobic therapeutic agent to be administered.

Double Patenting

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 35, 42-52, 54-61 and 65-82 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the composition claims of U.S. Patent Application Nos. 10/764,016 and 11/122,788.

The provisional rejection set forth over the composition claims of U.S. Patent Application No. 10/074,687 and 10/444,935 and the rejections set forth over the composition claims of U.S. Patent Nos.

6,451,339, 6,383,471, 6,309,663 and 6,267,985 have each been hereby **withdrawn** in view of reconsideration of the amended instant claims and the amended copending and/or patented claims.

Applicant traverses the rejections, stating that Applicant has not been apprised of the claims of the cited reference on which the rejection is based. Further, Applicant asserts that the instant claims are patentably distinct from the copending and/or patented claims.

Applicant is notified that the following claims are under rejection:

(1) For U.S. Patent Application No. 10/764,016: copending claims 1, 16-19, 21, 24, 32-33 and 37-43; and

(2) For U.S. Patent Application No. 11/122,788: copending claims 1, 3-31 and 33-34.

Further, Applicant has failed to provide any additional remarks or argument in support of the assertion that the instant claims are patentably distinct from the cited U.S. Patents and/or U.S. Patent Applications. Accordingly, and further in view of the absence of any Terminal Disclaimers in the record, the provisional and non-provisional obviousness-type double patenting rejections remain proper for the reasons of record set forth at pages 13-16 of the previous Office Action dated May 4, 2006, of which said reasons are herein incorporated by reference, and are hereby **maintained**.

Conclusion

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference WO 97/48382 to Mukai et al. entitled "Multiple-Unit Type Prolonged Action Drug Preparation".

Rejection of claims 35, 42-52, 54-61 and 65-82 is proper and is **maintained**.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leslie A. Royds
Patent Examiner
Art Unit 1614

April 27, 2007

Ardin H Marschel 4/29/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER